Rijetki sindromi u dječjoj i adolescentnoj psihijatriji: prikaz triju slučajeva

/ Rare Syndromes in Child and Adolescent Psychiatry: Three Case Reports

Marina Bježančević[1], Ivana Groznica Hržić[1], Zlatna Andraković[1], Vlatka Kovač[1,2], Stanislav Rogulja[1], Katarina Dodig-Ćurković[1,2,3]

[1]Sveučilište Josipa Jurja Strossmayera u Osijeku, Fakultet za dentalnu medicinu i zdravstvo, Osijek; [2]Sveučilište Josipa Jurja Strossmayera u Osijeku, Medicinski fakultet, Osijek; [3]Klinički bolnički centar Osijek, Zavod za dječju i adolescentnu psihijatriju, Osijek; Hrvatska

/ [1]*Josip Juraj Strossmayer University in Osijek,Faculty of Dental Medicine and Health;* [2]*Josip Juraj Strossmayer University in Osijek, Faculty of Medicine, Osijek;* [3]*Clinical Hospital Center Osijek, Department of Child and Adolescent Psychiatry, Osijek, Croatia*

U razdoblju od samo nekoliko mjeseci više slučajeva iznimno rijetkih sindroma upućeno nam je na psihijatrijsku procjenu i liječenje. U radu ćemo opisati naša iskustva u liječenju bolesnika sa sindromom Cornelia de Lange, Neuhauserovim sindromom i sindromom Incontinentia pigmenti. U kliničkoj slici smo zamijetili niz preklapajućih popratnih psihičkih obilježja kojima smo pristupili na jedinstven i individualizirani način. Prva smetnja u fokusu terapije bila je nesanica, intervencijom smo uspješno poboljšali trajanje i kvalitetu sna. Prisutne smetnje pažnje i koncentracije su ublažene provođenjem *neurofeedback* tretmana, koji je ujedno imao blagotvoran učinak na smanjenje učestalosti samoozljeđivanja, agresije prema drugima i iritabilnosti. Zaključno, psihijatrijskim liječenjem djece s rijetkim sindromima nastupilo je poboljšanje kvalitete života djeteta i obitelji, a multidisciplinarni pristup omogućio je pružanje optimalne razine skrbi unutar bolničkog sustava.

/ Over a period of a few months, several cases of extremely rare childhood syndromes were referred to us for psychiatric evaluation and treatment. We report three clinical cases with multiple overlapping psychological features: Cornelia de Lange, Neuhauser, and Incontinentia pigmenti syndrome. Each child was approached in a unique and individual way. The first issue considered in therapy was insomnia, and our intervention was effective, leading to improvements in duration as well as quality of sleep. Attention and concentration difficulties that were present were alleviated by neurofeedback treatment. At the same time, the treatment had a positive effect on the decrease of self-injury behavior, aggression, and irritability. To conclude, psychiatric treatment of children with rare syndromes improved the quality of life of the child and family, and the multidisciplinary approach provided the optimum level of care within the healthcare system.

ADRESA ZA DOPISIVANJE / *CORRESPONDENCE:*

Marina Bježančević, dr. med.

Zavod za dječju i adolescentnu psihijatriju

Klinički bolnički centar Osijek

Huttlerova 4

31 000 Osijek, Hrvatska

E-pošta: katarina5dodig@gmail.com

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SINDROM CORNELIA DE LANGE

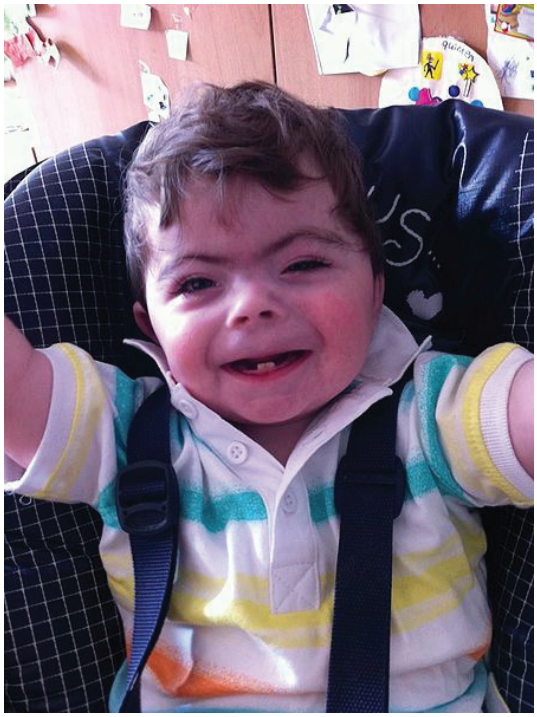
Cornelia de Lange je rijedak genetski poremećaj i kongenitalni sindrom koji je ime dobio po nizozemskoj pedijatrici Corneliji de Lange, a koja ga je prva opisala 1933. godine. Radi se o rijetkom sindromu, pojavljuje se u 1 na 10 000 djece, s jednakom učestalošću u oba spola i među svim rasama. Etiologija poremećaja je poznata. Godine 2004. otkrivena je mutacija gena NIPBL na 5. kromosomu (50 % slučajeva), zatim su otkrivene mutacije gena SMC1A, SMC3, HDAC8, RAD21 te je 2012. godine otkrivena mutacija gena HDAC8 na X kromosomu. Za rani probir koristi se ultrazvučni pregled u 18. tjednu trudnoće (promatra se dužina femura, nadlaktice i opseg glave) (1). Sindrom obuhvaća veliki raspon tjelesnih, kognitivnih, emocionalnih, psiholoških i razvojnih problema. Zajedničke tjelesne karakteristike novorođenčadi su: mala porođajna težina, mikrocefalija, spojene obrve, dugačke trepavice, mali nos, tanke usnice, pojačana dlakavost, kratke ruke i noge ili deformiteti ekstremiteta. Najčešći medicinski problemi s kojima se suočavaju ova djeca su: gastroezofagealni refluks, srčane mane, epilepsija, slabovidnost, nagluhost, deformiteti ekstremiteta, defekti građe nepca i zubi, kognitivne, ponašajne i govorne smetnje (2). Od psihičkih simptoma u literaturi se najčešće opisuju hiperaktivnost, anksioznost, depresija, problemi sa spavanjem, samoozljeđivanje i autoagresivno ponašanje (3). Prevalencija samoozljeđivanja kod ove djece je visokih 56 % i često je potaknuta gastrointestinalnim bolovima, bolnim zubom i sličnim bolnim stanjima. Kod ove djece pojavljuju se vrlo često problemi sa spavanjem i to od najranije dobi. Obično je riječ o smetnjama usnivanja te učestalim noćnim buđenjima. Prije psihijatrijskog liječenja poremećaja sna preporuča se isključivanje drugih mogućih somatskih i neuroloških uzroka. Apneja u snu je također česta pojava kod djece s Cornelia de Lange sindromom kada se savjetuje obrada otorinolaringologa, a ponekad i operacija krajnika (4,5).

CORNELIA DE LANGE

Cornelia de Lange is a rare genetic disorder and congenital syndrome named after the Dutch pediatrician Cornelia de Lange, who first described it in 1933. It is a rare syndrome, occurring in 1 out of 10 000 children, with equal frequency in both sexes and among all races. The etiology of the disorder is known. In 2004, a mutation of the NIPBL gene on the 5th chromosome was detected (in 50% of cases). In the following years, mutations of the SMC1A, SMC3, HDAC8, and RAD21 genes were detected. Lastly, the HDAC8 gene mutation on the X chromosome was detected in 2012. An ultrasound examination in the 18th week of pregnancy is used as early screening (femur length, upper arm and head circumference) (1). The syndrome consists of a wide range of physical, cognitive, emotional, psychological, and developmental issues. Some common physical characteristics of newborns are: low birth weight, microcephaly, eyebrows that meet in the middle, long lashes, a small nose, thin upper lip, hirsutism, short arms and legs, or limb deformities. The most common medical problems these children face include gastroesophageal reflux, heart defects, epilepsy, visual impairment, hearing loss, limb deformities, palate and teeth defects, and cognitive, behavioral, and speech difficulties (2). The most commonly reported psychiatric symptoms are hyperactivity, anxiety, depression, sleep problems, self-injury, and auto-aggressive behavior (3). Prevalence of self-injury behavior is at a high 56%, which is often triggered by gastrointestinal pain, toothache, and other pains. Sleep problems occur very often and from the earliest age. Usually, children have difficulties with falling asleep and/or frequent night waking. Before starting the psychiatric treatment, it is recommended to exclude other somatic and neurological causes of the present symptoms. Sleep apnea is also very common in children with Cornelia de Lange syndrome, and should be treated by an otolaryngologist (4,5).

Prikaz bolesnika

Dječak u dobi 8 godina dolazi prvi puta na pregled dječjem psihijatru u pratnji majke. Pohađa prvi razred po posebnom programu u specijalnoj školi, živi s roditeljima. U obiteljskoj anamnezi je negativan psihijatrijski hereditet. Dječak je rođen iz druge majčine trudnoće (prva trudnoća završila spontanim pobačajem). U 34. tjednu trudnoće zamijećen je zastoj u rastu ploda. Rođen je u terminu, prirodnim putem, Apgar skor 8/9. Odrasta kao jedino dijete u kompletnoj primarnoj obitelji. Rani psihomotorni razvoj je od rođenja bio usporen te je prohodao s 20 mjeseci, a prva riječ sa značenjem bila je u dobi od tri godine. U dojenačkoj dobi nakon kliničkog pregleda pedijatra i genetičke obrade postavljena je dijagnoza sindroma Cornelia de Lange. Govor nije u potpunosti uspostavljen, služi se pojedinačnim riječima i gestama. Nakon pete godine uspostavio je kontrolu stolice, a mokrenje i dalje ne kontrolira u potpunosti.



SLIKA 1. *Sindrom Cornelia de Lange* (Izvor: By Joris - Own work, CC BY-SA 3.0, dostupno na: https://commons.wikimedia.org/w/index.php?curid=30422316)
FIGURE 1. Cornelia de Lange syndrome (source: By Joris - Own work, CC BY-SA 3.0). Available at: https://commons.wikimedia.org/w/index.php?curid=30422316)

Case report

An 8-year-old boy was referred to a child and adolescent psychiatrist for an examination. He attended the first grade at a special school and lived with his parents. Family history was negative on psychiatric heredity. The boy was born from the mother's second pregnancy (her first pregnancy ended in miscarriage). In the 34th week of pregnancy, a stagnation in fetal growth was observed. He was a full-term baby, vaginaly delivered, with an Apgar score of 8 out of 9. He grew up as the only child, in a complete primary family. His early psychomotor development was delayed. He took his first steps at the age of 20 months, and spoke the first meaningful word at the age of three. After pediatric treatment and genetic screening, he was diagnosed with Cornelia de Lange syndrome. His speech is underdeveloped and he communicates using sounds, gestures, and single words. He achieved bowel control at the age of five, but has bladder control problems. He was vaccinated on the recommended schedule and did not have any of childhood communicable diseases. At the age of one, he had a heart surgery due to tetralogy of Fallot. He has autoimmune thrombocytopenia and leukopenia, hearing loss in both ears, gastroesophageal reflux, and *Helicobacter pylori* positive gastritis. At the age of five, he underwent an Achilles tendon surgery.

The boy was referred to us on the recommendation of his pediatrician. He had sleep difficulties since birth, struggled with falling asleep, and woke up frequently. His sleep intervals lasted one to two hours. His mother described him as hyperactive, with a short attention span of and sudden loss of interest, as well as poor eye contact. He communicated using gestures and a dozen words he knows (mom, dad, bye). He was dependent on continuous help, with assistance in daily self-care activities. He often presented auto-aggressive behavior when experiencing abdominal pain. He was well integrated into a special school, but occasionally wet his pants

Na tjelesnom planu redovito je cijepljen prema kalendaru cijepljenja, nije prebolio dječje zarazne bolesti. U dobi od godinu dana je imao operaciju srca zbog tetralogije Fallot. Zbog autoimune trombocitopenije i leukopenije prati ga hematolog, a zbog obostrane nagluhosti otorinolaringolog. U dobi od 5 godina je zbog deformiteta stopala i otežanog hoda operirao Ahilove tetive. U praćenju je i gastroenterologa zbog GERB-a i gastritisa (infekcija *Helicobacter pilory*), a operiran je i zbog impaktiranih zubi.

Dječak je upućen na pregled dječjem psihijatru po preporuci primarnog pedijatra zbog poteškoća sa spavanjem. Od rođenja jako teško zaspi, a kada spava budi se po nekoliko puta noću. San je u intervalima od sat do dva sata. Majka ga opisuje kao hiperaktivnog, vrlo brzo gubi interes, slabijeg je kontakta s okolinom, najviše voli šetati i motoričke aktivnosti. Komunicira pretežno gestama, koristi desetak riječi koje poznaje (mama, tata, baba, deda, papa...). Potreban mu je stalan nadzor u svim aktivnostima samozbrinjavanja. Često kada ima bolove u trbuhu pokazuje autoagresivno ponašanje. U specijalnoj školi se dobro uklopio, iako se povremeno u trenutcima protesta pomokri u gaćice. Tijekom pregleda dječak je bio vrlo uznemiren, kontakt se uspijevao uspostaviti kratkotrajno i površno, pažnja je bila lako otklonjiva, bio je nemiran, izlazio je van iz ambulante, majka ga je pokušavala smiriti fizičkim kontaktom. Kod dječaka su opservirane jasne karakteristične fizičke oznake sindroma Cornelia de Lange: mikrocefalija, spojene obrve, duge trepavice, nisko položene uške, nizak rast, pojačana dlakavost. Psihički simptomi bili su psihomotorni nemir, smetnje sa snom, agresivnost prema sebi i okolini, impulzivnost i nepredvidljivost u ponašanju. Nakon učinjenog psihijatrijskog intervjua, razgovora i savjetovanja s majkom preporučena je psihologijska procjena djeteta, tretman *neurofeedback* pod nadzorom dječjeg psihijatra i tretman radnog terapeuta. Od psihofarmakoterapije ordiniran je anksiolitik diazepam. Na kontrolnom pregledu koji je uslijedio nakon 2 tjedna opaženo je dis-

as a way of protesting. During the psychiatric examination, the boy was distressed, the eye contact was poor, he was easily distracted, and motorically very active, walking in and out of the room. His mother tried to calm him down using physical contact. Clear Cornelia de Lange syndrome characteristics could be observed: microcephaly, fused eyebrows, long lashes, delayed growth, increased hairiness. The psychiatric symptoms present were psychomotor agitation, sleep disorder, aggressive behavior, impulsiveness, and unpredictability in his actions. After the psychiatric interview, we counseled the mother and recommended a psychological assessment, neurofeedback treatment supervised by a child psychiatrist, and occupational therapy treatment. We also prescribed psychopharmacotherapy – an anxiolytic (diazepam). At 2-weeks follow-up, we observed some improvements: the patient was more calm, better at sleeping, and less auto-aggressive. Over the following month, the first results of neurofeedback therapy were noticed in the form of better concentration and attention. Involvement in occupational therapy resulted in reduction of daily frustrations, expanding the range of gestures and learning sign language.

NEUHAUSER SYNDROME

Neuhauser syndrome or megalocornea mental retardation (MMR) syndrome was first described in 1975 by the German neuropediatrician Gerhard Neuhäuser as a very rare congenital disorder characterized by megalocornea and neurological symptoms: intellectual disability, hypotonia, and epileptic seizures (6). Megalocornea is a bilateral, symmetric, non-progressive increase in horizontal corneal diameter greater than 12 mm in infants or greater than 13 mm in older children and adults, while ocular pressure remains normal. Apart from the increase, the corneas are of average thickness and do not have any histological changes. Af-

kretno poboljšanje u smislu da je psihomotorno mirniji, boljeg sna, manje autoagresivan prema sebi i okolini. U razdoblju od sljedećih mjesec i po dana počeli su se uočavati prvi rezultati *neurofeedback* terapije u smislu bolje koncentracije i pažnje te tretmana radnog terapeuta u obliku smanjivanja svakodnevnih frustracija povećavanjem opsega gesti i učenja znakovnog jezika.

NEUHAUSEROV SINDROM

Neuhauserov sindrom ili megalokorneja mentalna retardacija (MMR) sindrom je 1975. godine prvi puta opisao njemački neuropedijatar Gerhard Neuhäuser kao vrlo rijetki urođeni poremećaj karakteriziran megalokornejom i neurološkim simptomima - intelektualne teškoće, hipotonija i epileptički napadaji (6). Megalokorneja je bilateralno, simetrično, neprogresivno povećanje horizontalnog promjera rožnice većeg od 12 mm kod novorođenčeta ili većeg od 13 mm kod starije djece i odraslih, a očni tlak je normalan. Osim povećanja, rožnice su histološki neizmijenjene i prosječne debljine. Kod oboljele djece su prisutna dismorfična obilježja lica koja uključuju prominentno čelo, širok korijen nosa, epikantus, nisko položene uške, dugačak filtrum (7). U kliničkoj slici opisani su nerazvijen govor, stereotipni pokreti ruku, slab apetit, teškoće gutanja čvrste hrane. Do sada su opisana oko 37 bolesnika (prema podatcima NORD-a - Nacionalna organizacija za rijetke bolesti), više muških nego ženskih (8). Verloes i sur. su predložili kliničku klasifikaciju u podtipove (9). Etiologija nije u potpunosti razjašnjena, većina do sada opisanih slučajeva je konzistentna s autosomno recesivnim modelom nasljeđivanja ili *de novo* mutacijom. Fenotipska različitost upućuje na moguću genetičku heterogenost (10). Davidson i sur. su 2014. godine sekvencirali CHRDL1 gen i identificirali "*missense*" mutaciju kod X-vezane megalokorneje, no za ekstraokularne karakteristike nije nađena povezanost s istom mutacijom (11). Liječenje je multimodalno i usmjereno na specifične simptome koji su prisutni kod pojedinca.

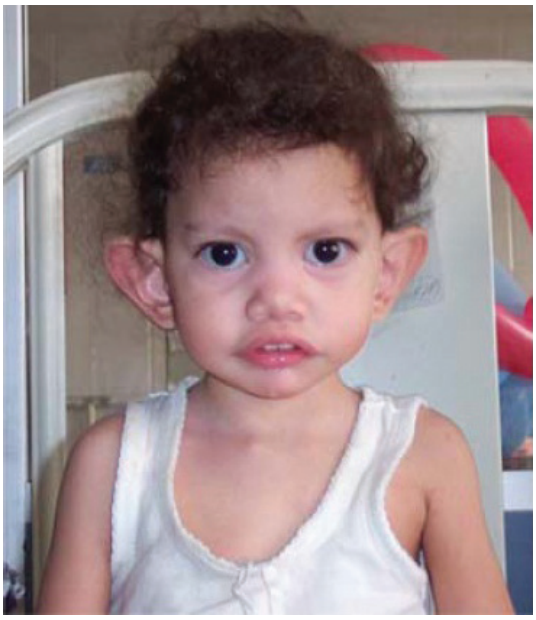
fected children have dysmorphic facial features: a prominent forehead, broad nose root, epicanthus, low-set ears, and long philtrum (7). Clinical presentation includes delayed speech, stereotypic hand movements, poor appetite, and difficulty swallowing solid food. According to NORD data (National Organization for Rare Disorders), about 37 patients have been described so far, of which more men than women (8). Verloes et al. suggested a clinical classification into subtypes (9). The etiology is still not fully understood, and most of the cases described so far are consistent with autosomal recessive inheritance model or *de novo* mutation. Phenotypic diversity indicates possible genetic heterogeneity (10). In the year 2014, Davidson et al. sequenced the CHRDL1 gene and identified a "missense" mutation in X-linked megalocornea, but the extraocular characteristics were not associated with the same mutation (11). Treatment is multimodal and focuses on the specific symptoms of every individual.

Case report

We report a case of a girl aged 10, who was attending a kindergarten group at a school for children with disabilities. She lived with her parents and sister and younger brother aged 9. The family had a positive psychiatric heredity. The father suffered from depression, post-traumatic stress disorder, and Type I diabetes mellitus. A younger brother aged 9 suffered from Neuhauser syndrome, while the sister has strabismus and the uncle has epilepsy. The patient was born from the mother's second twin pregnancy. In the 8th week of pregnancy, the mother was hospitalized for bleeding. The second fetus died at that time. She was treated with hormonal therapy. Before childbirth, an ultrasound examination showed growth failure. The child was born vaginally, and birth weight was low and the Apgar score was 7 out of 8. She was treated for perinatal infection. Ultrasound examination of the brain at 2 months showed

Prikaz bolesnika

Djevojčica u dobi od 10 godina, pohađa odgojno-obrazovnu skupinu u školi za djecu s posebnim teškoćama. Živi s roditeljima, sestrom i mlađim bratom u dobi od 9 godina. U obitelji je pozitivan psihijatrijski hereditet. Otac boluje od depresije, posttraumatskog stresnog poremećaja i od dijabetesa melitusa tip I. Mlađi brat u dobi od 9 godina boluje od Neuhauserova sindroma, sestra ima strabizam, ujak boluje od epilepsije. Djevojčica je rođena iz majčine druge blizanačke trudnoće, drugi plod je umro u 8. tjednu trudnoće. Tada je majka hospitalizirana zbog krvarenja i provođena je hormonska terapija. Neposredno prije poroda UZV pregledom ustanovljen je zastoj u rastu. Porod je bio u terminu prirodnim putem bez komplikacija, bovorođenče niske porođajne težine, Apgar 7/8. Zbog perinatalne infekcije zadržana je 2 tjedna na liječenju. UZV mozga u dobi od 2 mjeseca pokazao je asimetriju postraničnih komora. Zbog hipotonije provođene su vježbe medicinske gimnastike. Razvoj je bio usporen. Sjedila je u dobi od 1,5 godine, prohodala u dobi od 2 godine, kontrolu sfinktera uspostavila u dobi od 4 godine no još uvijek ima povremenu noćnu enurezu. Izgovarala je pojedinačne riječi, rečenice nije sklapala. Slabog apetita, sporije napredovala na tjelesnoj težini. Njene fenotipske karakteristike su normocefalična glava no dizmorfične stigme: hipertelorizam, epikantus, mongoloidno postavljeni očni rasporci, širi korijen nosa, naglašeni frontalni tuberi, otapostaza i mesnate uške, tanka gornja usna, šire razmaknuti zubi, hiperekstenzibilni zglobovi, promjer rožnica horizontalno 10 mm. U više navrata je hospitalizirana u specijalističkom centru za endokrinologiju i dijabetes gdje joj je postavljena dijagnoza. Iako djevojčica nema jedno od osnovnih obilježja sindroma - megalokorneju, ima prisutan niz drugih stigmi, a i bratu je ranije u istoj ustanovi dijagnosticiran Neuhauserov sindrom. U praćenju je neuropedijatra, logopeda, radnog terapeuta, oftalmolo-



SLIKA 2. Neuheuserov sindrom (Izvor: Avina-Fierro, JA i Hernandez-Avina, DA. Síndrome de Neuhauser: megalocórnea, retardo mental e hipotonía. Bol. Med. Hosp. Infant. Mex. 2008, vol.65, n.2, pp.135-137. dostupno na: http://www.scielo.org.mx/scielo.php?script=sci_arttext&pid=S1665-11462008000200008

FIGURE 2. Neuhauser syndrome (Source: Avina-Fierro, JA i Hernandez-Avina, DA. Síndrome de Neuhauser: megalocórnea, retardo mental e hipotonía. Bol. Med. Hosp. Infant. Mex. 2008, vol.65, n.2, pp.135-137. Available: http://www.scielo.org.mx/scielo.php?script=sci_arttext&pid=S1665-11462008000200008

asymmetry of lateral ventricles. She underwent physical therapy for hypotonia. Her development was delayed, and she started sitting at the age of 1.5 years, walking at the age of 2, and gained sphincter control at the age of 4, but with occasional night enuresis. She talked in single words instead of sentences, and had a poor appetite and low body weight. The patient presented following phenotypic characteristics: a normocephalic head, hypertelorism, epicanthus, eye positioning typical of Down syndrome, a broad nose root, accentuated frontal tubers, otapostasis and thick earlobes, a thin upper lip, broader spacing of teeth, hyperextensible joints, and a 10 mm horizontal corneal diameter. The patient was hospitalized on a number of occasions at a specialist center for endocrinology and diabetes where the diagnosis was established. Although the patient

ga. Zbog epileptičkih napadaja uzima terapiju uz koju nije imala napadaje već nekoliko godina. Na tjelesnom planu redovito je cijepljena prema kalendaru cijepljenja bez komplikacija, nije preboljela dječje zarazne bolesti.

Djevojčica dolazi na pregled dječjeg psihijatra po preporuci neuropedijatra zbog hiperaktivnosti, agresivnog ponašanja i nesanice. U odgojno-obrazovnoj skupini pretežito dobro funkcionira, a smetnje se javljaju unutar primarne obitelji te pri kontaktu izvan škole. U komunikaciji se služi gestama i izgovara nekoliko izoliranih riječi sa značenjem (mama, daj, pa-pa, am), odaziva se na svoje ime, izvršava jednostavne naloge, funkcionira na razini lake mentalne retardacije. Pokazuje interes za okolinu, prilazi drugim osobama i pokušava uspostaviti kontakt. Nesamostalna je u vještinama samozbrinjavanja. U trenutcima ljutnje i nezadovoljstva reagira heteroagresivno (udara, čupa, pljuje) te autoagresivno. Pri pregledu je bila motorički aktivna, nemirna, obilazila cijelu ambulantu. Opservirale su se povremene stereotipije u obliku pljeskanja. Kontakt se uspostavljao vrlo kratko i nedovoljno adekvatno za uspostavljanje komunikacije. Na prvu roditeljsku zabranu se počela rukama udarati po glavi i vrištati. Nakon iscrpnog intervjua, razgovora i savjetovanja preporučeno je uvođenje psihofarmakoterapije antipsihotikom risperidonom u niskoj dozi na koji dolazi do pomaka u smislu psihomotornog smirivanja, manje autoagresivnih i heteroagresivnih obrazaca u ponašanju, bolje dinamike sna. Preporučen je nastavak tretmana logopeda i radnog terapeuta te uključivanje u *neurofeedback* tretmane. Obitelj je suradljiva, no rehabilitacijski tretman je otežan zbog udaljenosti njihovog mjesta stanovanja.

SINDROM *INCONTINENTIA PIGMENTI*

Incontinentia pigmenti je vrlo rijetka, nasljedna i multisistemska bolest. Naziva se i Bloch-Sulzbergerov sindrom (Bloch 1926., Sulzberger

did not present one of the basic features of the syndrome – megalocornea – there were a number of other stigma present, and her brother was previously diagnosed with Neuhauser syndrome. She was received multidisciplinary treatment from the following specialists: a neuropediatrician, speech therapist, ophthalmologist, and occupational therapist. She regularly takes antiepileptics and has not had an epileptic seizure for several years now. She has been regularly immunized with vaccines without complications, and did not have any childhood communicable diseases.

The girl was referred to a psychiatric examination at the recommendation of a neuropediatrician because of symptoms that included hyperactivity, aggressive behavior, and insomnia. The patient functioned well in her school group, and most of her behavioral problems occurred at home and outside the school. She communicates with gestures and only speaks a few words with meaning ("mom, give, bye, yummy"), responds to her own name, executes simple orders, and functions at the level of mild intellectual disability. She shows interest in the environment, approaches other people, and tries to establish contact. She requires help with daily self-care activities. During periods of anger and dissatisfaction, the patient reacts aggressively (strikes, spits) and auto-aggressively. During the examination, she was motorically very active and restless. Occasional stereotypical movements in the form of applause were observed. Contact with the patient could only be established very briefly and insufficiently to establish communication. At the first instance of the parent forbidding something, she began hitting herself and screaming. After our interview and counseling, we recommended introduction of psychopharmacology – antipsychotic risperidone at a low dose for achieving psychomotor calming, less aggressive behavior, and better sleep. We recommended to continuing treatment with speech therapists

1925.). U znanstvenoj literaturi zabilježeno je između 900 i 1200 oboljelih. Kliničke manifestacije su vrlo varijabilne, no uvijek su udružene s promjenama kože. Prenosi se kao X-vezano dominantno svojstvo i javlja se gotovo isključivo kod djevojčica (u 95 % oboljelih). U većini slučajeva prenatalno je smrtonosna za mušku djecu. Etiologija je poznata, radi se o mutacijama IKBKG gena koji daje upute za izradu proteina koji pomaže regulirati nuklearni faktor-kappa-B (zaštita stanica od samouništenja) (12). Kod žena neke stanice proizvode normalnu količinu IKBKG proteina, a druge stanice ga ne proizvode, pa dobivena neravnoteža dovodi do znakova i simptoma ove bolesti. Kod muškaraca većina IKBKG mutacija dovodi do potpunog gubitka IKBKG proteina što se čini da je smrtonosno u ranom razvoju. Pogođeni muškarci koji prežive mogu imati IKBKG mutaciju s relativno blagim učincima, IKBKG mutaciju samo u nekim dijelovima tijela (mozaicizam) ili dodatnu kopiju X kromosoma u svakoj stanici. Neki ljudi s inkontinencijom pigmenta nasljeđuju IKBKG mutaciju od jednog pogođenog roditelja, dok su drugi slučajevi rezultat novih mutacija u genu i javljaju se kod osoba bez povijesti poremećaja u njihovoj obitelji. Bolest je obilježena pojavom malformacija i anomalija kože, kose, noktiju, zuba, očiju i središnjeg živčanog sustava. Klinička slika se manifestira tijekom ranog neonatalnog razdoblja i započinje upalnim promjenama epidermisa (eritem, bule) koje prolaze do 6. mjeseca života. Nakon te faze slijedi tzv. pigmentni stadij u obliku nastajanja prljavosmeđih nepravilnih hiperpigmentacija, obično glutealno i na bočnim dijelovima tijela i ekstremiteta. Kod 50 % slučajeva opisane su i anomalije središnjeg živčanog sustava, očiju, zubi i skeleta. Razlikujemo dva tipa: učestaliji klasični tip bolesti (IP tip 2 ili obiteljski tip), koji je smrtonosan za mušku djecu, te drugi mnogo rjeđi sporadičan tip (IP tip 1) u starijoj literaturi poznat kao hipomelanoza po Itu. IP tip 2 je uzrokovan mutacijom gena NEMO koji se nalazi na xq28, a IP1 kao posljedica *de novo* mutacije na xp11 regiji (13).

and occupational therapists as well as starting neurofeedback treatments. The family was collaborative, but rehabilitation treatment was difficult for them to maintain because of the long distance from their home.

INCONTINENTIA PIGMENTI

Incontinentia pigmenti or Bloch-Sulzberger's syndrome (Bloch 1926, Sulzberger 1925) is a very rare, hereditary, and multisystem disease. There have been between 900 and 1200 patients reported in the scientific literature. Clinical manifestations are highly variable, but are always associated with skin changes. It is inherited as an X-related dominant feature and occurs almost exclusively in women (in 95% of patients). In most cases, the syndrome has a prenatal deadly outcome for male children. The etiology is known, and mutations have been found in the IKBKG gene, which provides instructions for build-up of the proteins that help regulate nuclear factor kappa-B (cell protection from self-destruction) (12). In women, some cells produce a normal amount of IKBKG protein while other cells do not produce any, so the resulting imbalance leads to the signs and symptoms of this syndrome. In men, most IKBKG mutations lead to complete loss of IKBKG protein, which seems to be deadly in the early development. Affected surviving men may have an IKBKG mutation with relatively mild effects, IKBKG mutation only in some parts of the body (mosaicism), or an additional copy of the X chromosome in each cell. Some people with incontinentia pigmenti inherit the IKBKG mutation from one affected parent, while other cases are the result of new mutations in the gene and occur in people with no history of the disorder in their family. The syndrome is characterized by malformations and anomalies of the skin, hair, nails, teeth, eyes, and the central nervous system. Clinical symptoms present themselves during the early neonatal

Prikaz bolesnice

Djevojčica u dobi od 4 godine i 8 mjeseci živi s obitelji. Rođena je u terminu, sekcijom, kao najmlađa od troje djece. Nije progovorila, nije prohodala niti uspostavila kontrolu sfinktera. U neuropedijatrijskom je liječenju zbog Bloch-Sulzbergerovog sindroma i zaostajanja u razvoju, dizmorfije glave i lica, malformacija središnjeg živčanog sustava, deformacija dijelova tijela, promjena kože, pretrpjela je i moždani inzult. Zbog epilepsije uzima antiepileptike. Kontinuirano je uključena u habilitacijski program.

Dolazi na pregled dječjeg psihijatra po preporuci neuropedijatra zbog smetnji u obliku iritabilnosti, povremene psihomotorne agitacije te povremenih teškoća usnivanja. Pri pregledu je uspostavila kontakt, smiješila se, bila živahna, nije govorila, vokalizirala je, nije bila pokretna nego

SLIKA 3. *Incontinentia pigmenti* (Izvor: Osório, F., Magina, S., Nogueira, A., & Azevedo, F. (2010). Incontinentia Pigmenti with vesicular stage. Dermatology Online Journal, 16(10). Dostupno na: https://escholarship.org/uc/item/9dz2p5bk
FIGURE 3. Incontinentia pigmenti (source: Osório, F., Magina, S., Nogueira, A., & Azevedo, F. (2010). Incontinentia Pigmenti with vesicular stage. Dermatology Online Journal, 16(10). Available at: https://escholarship.org/uc/item/9dz2p5bk

period, starting with inflammatory changes in the epidermis (erythema, bullae) that last up to 6 months of age. That phase is followed by the so-called pigment stage in the form of brown irregular hyperpigmentations, usually with gluteal and lateral localization on the body and extremities. In 50% of cases, anomalies of the central nervous system, eyes, teeth, and skeleton are also described. There are two types of the syndrome, a more common type (IP type 2 or the familial type) that is deadly for male fetuses and the other sporadic and rare type (IP type 1) – known as hypomelanosis of Ito in the older literature. IP type 2 is caused by mutation of the NEMO gene located at xq28, while IP1 is the result of *de novo* mutation in the xp11 region (13).

Case report

The patient was a girl aged 4 years and 8 months, living with her family. She was born in term and delivered via cesarean section, as the youngest of three children. Her development was delayed and she did not speak or walk and does not have sphincter control. From early on, she received treatment by a neuropediatrician due to a diagnosis of incontinentia pigmenti (Bloch-Sulzberger's syndrome). Some of her features and symptoms were: head and face dysmorphia, central nervous system malformations, deformation of some body parts, skin changes, and past cerebral insult. She is taking antiepileptics for epilepsy and is continuously involved in a habilitation program.

The patient was referred to an examination by a child psychiatrist at the recommendation of a neuropediatrician due to difficulties including irritability, occasional psychomotor agitation, and sleep problems. During the examination, eye contact could be made, the patient was smiling, and while she did not speak in words she communicated with vocalizations. The patient was in a wheelchair. We started with

u kolicima. Preporučen je *neurofeedback* tretman. Obitelj je suradljivo započela dolaženjem na tretmane više puta na tjedan. Nakon nekoliko mjeseci i dva provedena *neurofeedback* ciklusa djevojčica je ublažene iritabilnosti, smanjenog psihomotornog nemira, bolje regulacije sna.

KRATKA RASPRAVA I ZAKLJUČAK

Rijetki sindromi u dječjoj dobi, unatoč svojoj specifičnoj kliničkoj slici, često ostanu dugi niz godina neprepoznati. Rana dijagnoza je vrlo važna, kako bi se što ranije moglo započeti rehabilitacijom i kako bi se omogućilo da dijete dosegne svoj puni potencijal sa što manje deficita bilo koje vrste. U primjerima naša tri prikazana slučaja djeca su već više godina imala postavljenu dijagnozu sindroma, a obitelji su prihvatile bolest i njena ograničenja. Stoga naglasak ipak nije bio na prepoznavanju sindroma i upućivanju na pedijatrijsku obradu. Djeca su se javljala na dječju psihijatriju zbog popratnih psihičkih smetnji koje su relativno često prisutne, a javljaju se u različitom stupnju ovisno o pojedinom sindromu i njegovoj težini. Psihijatrijsko liječenje djece s rijetkim sindromima nije pravilo, a često nije niti praksa. U našim slučajevima imali smo iznimno dobru suradnju s pedijatrima. Jedno od prikazane djece nam je bilo upućeno od primarnog pedijatra, a dvoje od neuropedijatara, koji su prepoznali važnost multidisciplinskog pristupa i s kojima smo u tijeku daljnjeg liječenja zadržali dobru suradnju. Obitelji su bile iscrpljene dugotrajnošću tih smetnji. Zajedničke smetnje na psihičkom planu bile su: psihomotorni nemir, iritabilnost, impulzivnost, poremećaji spavanja, sniženi prag tolerancije na frustrativne podražaje, autoagresija i heteroagresija, deficiti pažnje, nizak intelektualni kapacitet, regresivno ponašanje, usporen razvoj govora ili potpuni izostanak govora. Roditelji su se u prvom redu žalili na poremećaje spavanja (otežano uspavljivanje, često noćno buđenje, nesanica), simptome koji imaju direktan utjecaj i na roditeljsko spavanje vodeći

a neurofeedback treatment. After several months and two neurofeedback cycles, irritability and psychomotor agitation were reduced and sleep was much better regulated.

SHORT DISCUSSION AND CONCLUSION

Rare childhood syndromes, despite their specific clinical presentation, often remain unidentified for many years. Early diagnosis is very important in order to begin with rehabilitation as early as possible, to help children reach their full potential and minimize deficits of any kind. In our three cases, the children had already been diagnosed several years ago, and their families have accepted the syndrome and its limitations. The emphasis was therefore not on recognizing the syndrome and referral to pediatric treatment. The children had been referred to child psychiatry because of the concomitant psychiatric symptoms that are relatively common and occur in a wide range and severity. Psychiatric treatment is not the rule and is often not the practice. In our cases, we had exceptionally good co-operation with pediatricians. One of the children was sent to us on the recommendation of the primary pediatrician, and two children on the recommendation of the neuropediatrician, who recognized the importance of the multidisciplinary approach. We maintained good co-operation in the course of treatment. The families were exhausted by the long-lasting nature of these symptoms: psychomotor agitation, irritability, impulsiveness, sleep disturbances, reduced tolerance to frustration, auto- and hetero-aggressive behavior, attention deficits, intellectual disability, regressive behavior, and delayed speech. The parents were primarily concerned about sleep issues (difficulty falling asleep, recurrent night waking, insomnia), which have a direct impact on parental sleep, leading to chronic exhaustion and reduction in the quality of life.

do kronične iscrpljenosti i slabljenja kvalitete života cijele obitelji. Tim popratnim psihičkim obilježjima pristupili smo na visoko individualizirani način proširivajući preporuke za tretman na dostupne stručne službe unutar našeg sustava. Primarna smetnja u sva tri slučaja bila je nesanica, koja se relativno brzo i uspješno uklonila, u dva slučaja farmakološkom intervencijom, a u trećem slučaju učinkom *neurofeedback* tretmana. U sva tri slučaja smo započeli zbog smetnji pažnje i koncentracije te iritabilnosti *neurofeedback* tretmanom. Uključivanje u *neurofeedback* tretmane ima za svrhu poboljšanje kognitivnih sposobnosti (pažnja), emocionalne kontrole (smanjenje anksioznosti) i psihofizičkog funkcioniranja (smanjivanje psihomotorne pobuđenosti). Roditelji su bili izrazito suradljivi, dovodili dijete na tretman 2 ili 3 puta tjedno, te je njihovim angažmanom *neurofeedback* mogao biti adekvatno provođen. Rezultati koji su uslijedili trajanjem tretmana nisu samo ublažili ciljane smetnje, već smo zamijetili i blagotvorno djelovanje na smanjenje autoagresije i agresivnog ponašanja općenito. U svrhu sveobuhvatnijeg liječenja proširili smo preporuke za tretman radnog terapeuta. Radnom terapijom se utječe na bolje savladavanje aktivnosti samozbrinjavanja što smanjuje potrebu za neprekidnom pomoći druge osobe. Kod zaostajanja govora (sva tri naša slučaja) uči se modificirani znakovni jezik, što povećava načine komunikacije i kod djeteta vodi do osjećaja bolje povezanosti i manje frustracija.

Zaključno, psihijatrijskim liječenjem djece s rijetkim sindromima nastupilo je poboljšanje kvalitete života djeteta i cijele obitelji, a multidisciplinski pristup doveo je do pružanja najbolje moguće razine liječenja unutar bolničkog sustava.

We approached the treatment of these psychological features in a highly individualized way, extending our treatment recommendations to other healthcare professionals within our department and hospital.

The first issue considered in therapy in all three cases was insomnia, which was relatively quickly and successfully eliminated, in two cases by pharmacological intervention and in the third case with the effect of neurofeedback treatment. Our intervention was effective, leading to improvements in duration as well as quality of sleep. Due to attention and concentration difficulties present in all three cases, we started with neurofeedback treatment. We aimed to improve cognitive abilities (attention), emotional control (anxiety reduction), and psychophysical functioning (reduction of psychomotor agitation). The treatment had a positive effect by alleviating those issues, and we also observed a decrease in self-injury behavior, aggression, and irritability. The parents were highly collaborative, bringing the child to treatment 2 or even 3 times a week. The children were also involved in occupational therapy, which has an effect on improving self-care skills and helping the children become less dependent on the help of other people and by teaching them sign language, expanding ways to communicate and to feel more connected and less frustrated.

In conclusion, psychiatric treatment of children with rare syndromes improved the quality of life of the children and their family, and the multidisciplinary approach provided the optimum level of care within the healthcare system.

LITERATURA / *REFERENCES*

1. Basile E, Villa L, Selicorni A, Molteni M. The behavioral phenotype of Cornelia de Lange Syndrome: a study of 56 individuals. J Intellect Disabil Res 2007; 51: 671-81.
2. Berney T, Ireland M, Burn J. Behavioral phenotype of Cornelia de Lange syndrome, Arch Dis Child 1999; 81(4): 333-6.
3. Hall SS, Arron K, Sloneem J, Oliver C. Health and sleep problems in Cornelia de Lange Syndrome: a case control study. J Intellect Disabil Res 2008; 52: 458-68.

4. Kline A. Clinical delineation of sleep disturbance in Cornelia de Lange syndrome. American Society of Human Genetics, Annual meeting, 2007.
5. web stranica: www.cdlsusa.org
6. Neuhauser G, Kaveggia EG, France TD, Opitz JM. Syndrome of mental retardation, seizures, hypotonic cerebral palsy and megalocorneae, recessively inherited. Ztschr Kinderheilkunde 1975; 120: 1-18.
7. Meire FM. Megalocornea. Clinical and genetic aspects. Documenta ophthalmologica. Advances in Ophthalmology 1994; 87: 1-121.
8. web stranica: www.rarediseases.org
9. Verloes A, Journel H, Elmer C, Messon JP, Le Merrer M, Kaplan J *et al*. Heterogeneity versus variability in megalocornea-mental retardation (MMR) syndromes: report of new cases and delineation of 4 probable types. Am J Med Genet 1993; 46(2): 132-7.
10. Gutierrez-Amavizca BE, Juarez-Vazquez CI, Orozco-Castellanos R, Arnaud L, Macias-Gomez NM, Barros Nunez P *et al*. Neuhauser syndrome: a rare association of megalocornea and mental retardation. Review of the literature and further phenotype delineation. Genet Couns 2013; 24: 185-91.
11. Davidson AE, Cheong S-S, Hysi PG, Venturini C, Plagnol V, Ruddle JB *et al*. Association of CHRDL1 Mutations and Variants with X-linked Megalocornea, Neuhauser Syndrome and Central Corneal Thickness, PLoS ONE 2014; 9(8): e104163.
12. Swinney CC, Dennis PH, Karth PA. Incontinentia Pigmenti: A Comprehensive Review and Update, Ophthalmic Surgery, Lasers & Imaging Retina 2015; 46(6): 650-7.
13. Scheuerle AE, Ursini MV. Incontinentia Pigmenti. 1999 Jun 8 [Updated 2017 Dec 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Dostupno na: https://www.ncbi.nlm.nih.gov/books/NBK1472/